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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/JP99/02192 <b>(22) International Filing Date:</b> 26 April 1999 (26.04.99)  <b>(30) Priority Data:</b> 10/136126 29 April 1998 (29.04.98) JP  <b>(71) Applicant (for all designated States except US):</b> SUMITOMO PHARMACEUTICALS CO., LTD. [JP/JP]; 2-8, Doshomachi 2-chome, Chuo-ku, Osaka-shi, Osaka 541-8510 (JP).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> NISHII, Hiroyuki [JP/JP]; 9-1-404, Tamagawa 1-chome, Takatsuki-shi, Osaka 569-0857 (JP). KOBAYASHI, Hirohisa [JP/JP]; 12-10, Nakatsu-cho, Ibaraki-shi, Osaka 567-0824 (JP). OTODA, Kazuya [JP/JP]; 1-10, Nakayama-sakuradai 5-chome, Takarazuka-shi, Hyogo 665-0877 (JP).  <b>(74) Agent:</b> NAKAMURA, Toshio; Sumitomo Pharmaceuticals Co., Ltd., Intellectual Property Dept., 1-98, Kasugadenaka 3-chome, Konohana-ku, Osaka-shi, Osaka 554-0022 (JP).		<b>(81) Designated States:</b> AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> ORAL FORMULATION COMPRISING BIGUANIDE AND AN ORGANIC ACID  <b>(57) Abstract</b>  An oral formulation comprising a biguanide and an organic acid has less unpleasant tastes such as bitterness and saltiness.		

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## DESCRIPTION

### ORAL FORMULATION COMPRISING BIGUANIDE AND AN ORGANIC ACID

#### 5 TECHNICAL FIELD

The present invention relates to an oral fomulation comprising a biguanide and an organic acid.

#### BACKGROUND OF THE INVENTION

10 Biguanides such as metformin have unpleasant tastes such as bitterness and saltiness. The dosages of metformin are about 250 mg per dose in Japan and about 850 mg per dose in United States of America. In spite of such big dosages, only tablets are on sale at present.

15 There are several known methods for masking bitterness of bitter drugs, for instance, for solid formulations, sugar coated tablets, film coated tablets, capsules and the like are useful. Powders, fine granules and granules are formulated with sweetening agents or flavors; microcapsules, non-enteric coated formulation, 20 spray-dried formulation with low melting point wax, formulation with lecithin (JP 62-265234-A) and the like may also be used. For solutions, there are formulations with water-insoluble high molecular weight compound such as ethylcellulose and hydroxypropylmethylcellulose phthalate (JP 52-41214-A); formulations 25 with acidic phospholipids or lyso-phospholipids (JP 7-67552-A); and formulations with a large amount of citric acid (JP 4-58452-B).

#### DISCLOSURE OF THE INVENTION

The inventors of the present invention have intensively carried

out research, and found that an oral formulation comprising a biguanide and an organic acid has less unpleasant tastes such as bitterness and saltiness. Thus, the present invention has been accomplished.

5

The present inventions includes:

[1] An oral formulation comprising a biguanide and an organic acid.

10

[2] An oral formulation comprising a biguanide, an organic acid and a sweetening agent.

[3] An oral formulation according to [1] or [2] wherein the biguanide is metformin or a pharmaceutical salt thereof.

15

[4] An oral formulation according to any one of [1] to [3] wherein the organic acid is malic acid, citric acid, tartaric acid or mixture thereof.

[5] An oral formulation according to any one of [1] to [4] wherein the sweetening agent is aspartame<sup>TM</sup>, saccharine, saccharine sodium, stevioside or mixture thereof.

20

[6] An oral formulation according to any one of [1] to [5] wherein the ratio (w/w) of the biguanide to the organic acid is 1 : 0.01 to 1 : 50.

[7] An oral formulation according to any one of [2] to [6] wherein the ratio (w/w) of the biguanide to the sweetening agent is 1 : 0.001 to 1 : 10

25

[8] An oral formulation according to any one of [1] to [7] wherein the formulation is solution, jelly, gum drops, dry syrup, powders, fine granules or granules.

[9] An oral formulation according to any one of [1] to [8] wherein the pH of the solution is 3.5 to 6 in case that the

formulation is solution, and the pH of the solution which is formed by dissolving or dispersing the formulation to 10 times more (w/w) volume of water, is 3.5 to 6 in case that the formulation is not solution.

5

#### DETAILED DESCRIPTION OF THE INVENTION

"Biguanide" includes compounds having a biguanide structure such as metformin, buformin, fenformin and pharmaceutically acceptable salts thereof.

10

"Organic acid" includes malic acid, citric acid, tartaric acid, ascorbic acid, succinic acid, fumaric acid, maleic acid, gluconic acid, glucuronic acid and mixtures thereof. Preferable organic acids are organic acids having 2 or 3 carboxyl groups such as malic acid, citric acid and tartaric acid, more preferably malic acid.

15

The ratio (w/w) of the biguanide to the organic acid is, for example, 1 : 0.01 to 1 : 50, preferably 1 : 0.02 to 1 : 10, more preferably 1 : 0.05 to 1 : 1. In the case of malic acid, the preferable ratio (w/w) of the biguanide to malic acid is 1 : 0.05 to 1 : 0.5.

20

"Sweetening agent" includes aspartame<sup>TM</sup>, saccharin, saccharin sodium, stevioside, *sormatin*, erythritol, sorbitol, xylitol, glycerin and mixtures thereof. Preferable sweetening agents are aspartame<sup>TM</sup>, saccharin, saccharin sodium and stevioside. The ratio (w/w) of the biguanide to the sweetening agent is, for example, 1 : 0.001 to 1 : 10, preferably 1 : 0.02 to 1 : 1.

25

When the formulation is a solution, preferably the pH of the solution is 3.5 to 6, more preferably 4 to 6, to decrease the unpleasant tastes and to keep the biguanide stable. If the formulation is not a solution, the preferable pH of the solution or

dispersion which is formed by dispersing the formulation in water (1 part of the formulation to 10 parts of water, by weight), is 3.5 to 6, more preferably 4 to 6; This is in order to decrease the unpleasant tastes and to keep the biguanide stable.

5

"Oral formulation" includes solution, jelly, gum drops, dry syrup, powders, fine granules and granules. Preferably the formulation is not in the form of tablets.

10

The formulation of the present invention may include pharmaceutically acceptable non-toxic and inactive additives. Additives include excipients such as corn starch, potato starch, white sugar, mannitol, xylitol, sorbitol, talc, kaolin, calcium monohydrogen phosphate, calcium sulfate, calcium carbonate, crystalline cellulose; lubricants such as magnesium stearate and potassium stearate; disintegrators such as carboxymethylcellulose calcium and low substituted hydroxymethylcellulose; binders such as hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, gelatin, methylcellulose, Arabia gum and polyvinylalcohol; coloring agents; correctives; adsorbents; preservatives; stabilizers; moistening agents; de-charging agents; pH adjusters; and the like.

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The formulation may include flavors such as lemon, orange, grapefruit, pine, banana, chocolate and yogurt to decrease the unpleasant tastes more.

The formulation of the present invention can be prepared by well known methods. In the case of solid formulations, the formulation can be prepared, for example, by extruding granulation

methods, crushing granulation methods, dry granulation methods, fluidized bed granulation methods, tumbling granulation methods, high shear mixing granulation methods, wet compression methods, direct compression methods and the like.

5

The formulation of the present invention will contain the conventional amounts of active ingredient (biguanide) and will be used in conventional manner to administer doses in accordance with normal practice by routes and according to dosage regimes which are familiar to pharmacologists and medical practitioners.

10

The present invention will be described in detail below, referring to Examples and Experiments, which are not limitative of the present invention.

15

#### Example 1

##### Solution of metformin hydrochloride

	Ingredient	weight %
	-----	
20	Metformin hydrochloride	5 %
	Malic acid	0.8 %
	Aspartame <sup>TM</sup>	0.3 %
	Lemon flavor	0.1 %
	Purified water	93.8 %

25

5 % Solution of metformin hydrochloride is prepared by dissolving metformin hydrochloride, malic acid, aspartame<sup>TM</sup> and lemon flavor into purified water.

#### Example 2

Solution of metformin hydrochloride

	Ingredient	weight %
	-----	
	Metformin hydrochloride	5 %
5	Malic acid	0.8 %
	Saccharin sodium	1 %
	Lemon flavor	0.1 %
	Purified water	93.1 %

5 % Solution of metformin hydrochloride is prepared by  
10 dissolving metformin hydrochloride, malic acid, saccharine sodium  
and lemon flavor into purified water.

## Example 3

Solution of metformin hydrochloride

15	Ingredient	weight %
	-----	
	Metformin hydrochloride	5 %
	Citric acid	2 %
	Aspartame <sup>TM</sup>	0.3 %
20	Lemon flavor	0.1 %
	Purified water	92.6 %

5 % Solution of metformin hydrochloride is prepared by  
dissolving metformin hydrochloride, citric acid, aspartame<sup>TM</sup> and  
lemon flavor into purified water.

25

## Example 4

Solution of metformin hydrochloride

Ingredient	weight %
-----	

	Metformin hydrochloride	5 %
	Malic acid	1.5 %
	Saccharin sodium	0.25 %
	Erythritol	10 %
5	Lemon flavor	0.1 %
	Purified water	83.15 %

5 % Solution of metformin hydrochloride is prepared by dissolving metformin hydrochloride, malic acid, saccharin sodium, erythritol and lemon flavor into purified water.

10

#### Example 5

##### Solution of metformin hydrochloride

	Ingredient	weight %
	-----	
15	Metformin hydrochloride	5 %
	Malic acid	1.5 %
	Aspartame <sup>TM</sup>	0.2 %
	Sorbitol	6 %
	Grapefruit flavor	0.1 %
20	Purified water	87.2 %

5 % Solution of metformin hydrochloride is prepared by dissolving metformin hydrochloride, malic acid, aspartame<sup>TM</sup>, sorbitol and grapefruit flavor into purified water.

#### 25 Example 6

##### Solution of metformin hydrochloride

	Ingredient	weight %
	-----	
	Metformin hydrochloride	5 %

	Malic acid	1.5 %
	Saccharin	0.03 %
	Glycerin	10 %
	Lemon flavor	0.1 %
5	Purified water	83.37 %

5 % Solution of metformin hydrochloride is prepared by dissolving metformin hydrochloride, malic acid, saccharin, glycerin and lemon flavor into purified water.

10 Example 7

Solution of metformin hydrochloride

	Ingredient	weight %
	-----	
	Metformin hydrochloride	5 %
15	Malic acid	1.5 %
	Saccharin sodium	0.25 %
	Saccharin	0.03 %
	Lemon flavor	0.1 %
	Purified water	93.12 %

20 5 % Solution of metformin hydrochloride is prepared by dissolving metformin hydrochloride, malic acid, saccharin sodium, saccharin and lemon flavor into purified water.

Example 8

25 Dry syrup of metformin hydrochloride

	Ingredient	Amount
	-----	
	Metformin hydrochloride	500 g
	Malic acid	80 g

Saccharin sodium	25 g
Erythritol	865 g
Polyvinylpyrrolidone K30	30 g

5                                      Total                                      1500 g

Metformin hydrochloride, malic acid, saccharin sodium, erythritol and polyvinylpyrrolidone K30 are mixed with 200 g of mixture of purified water and ethanol (1 : 1 (w/w)) to give wet solid. 33 % Dry syrup of metformin hydrochloride is prepared by  
 10                                      milling the wet solid with a granulation mill to adjust the size of the granules, followed by drying.

#### Example 9

##### Jelly of metformin hydrochloride

15	Ingredient	weight %
	-----	
	Metformin hydrochloride	5 %
	Gelatin	0.5 %
	Malic acid	0.8 %
20	Aspartame <sup>TM</sup>	0.3 %
	Lemon flavor	0.1 %
	Purified water	93.3 %

Jelly of metformin hydrochloride is prepared by dissolving or dispersing metformin hydrochloride, malic acid, aspartame<sup>TM</sup> and  
 25                                      lemon flavor into gelatin solution which is made by dissolving gelatin to purified water over 80 °C, followed by cooling.

#### Example 10

##### Fine granules of buformin hydrochloride

	Ingredient	Amount
	-----	
	Buformin hydrochloride	100 g
	Mannitol	300 g
5	Lactose	300 g
	Corn starch	150 g
	Malic acid	90 g
	Aspartame <sup>TM</sup>	30 g
	Methylcellulose	30 g
10	-----	
	Total	1000 g

Buformin hydrochloride, mannitol, lactose, corn starch, malic acid, aspartame<sup>TM</sup> and methylcellulose are mixed with 200 g of purified water to give wet solid. 10 % Fine granules of buformin hydrochloride are prepared by granulating the wet solid with a basket granulation mill, followed by drying.

#### Example 11

##### Gum drops of buformin hydrochloride

20	Ingredient	Amount
	-----	
	Buformin hydrochloride	100 mg
	Gelatin	600 mg
	Citic acid	100 mg
25	Saccharin sodium	25 mg
	Sorbitol	1550 mg
	Lemon flavor	25 mg
	Purified water	600 mg
	-----	

Total 3000 mg

Gum drops of buformin hydrochloride are prepared by dissolving or dispersing buformin hydrochloride, citric acid, saccharin sodium, sorbitol and lemon flavor into gelatin solution which is made by  
 5 dissolving gelatin to purified water over 80 °C, followed by molding the mixture and cooling.

### Example 12

#### Powders of buformin hydrochloride

10	Ingredient	Amount
	-----	
	Buformin hydrochloride	100 mg
	Mannitol	560 mg
	Corn starch	200 mg
15	Citric acid	100 mg
	Aspartame <sup>TM</sup>	30 mg
	Magnesium stearate	10 mg
	-----	
	Total	1000 mg

20 10 % powders of buformin hydrochloride are prepared by mixing buformin hydrochloride, mannitol, corn starch, citric acid, aspartame<sup>TM</sup> and magnesium stearate.

### Example 13

#### 25 Solutions of metformin hydrochloride at various pH

Using the same amount of each ingredient of Example 1, 5 % solutions of metformin hydrochloride at various pH are prepared by dissolving or dispersing metformin hydrochloride, malic acid, aspartame<sup>TM</sup> and lemon flavor into about 80 % of purified water,

followed by adjusting pH of the solution to pH 2, 3, 3.5, 4, 5 or 6 using dilute hydrochloric acid or dilute sodium hydroxide solution and adding more purified water.

# 5 Reference example 1

## Solution of metformin hydrochloride

	Ingredient	weight %
	-----	
	Metformin hydrochloride	5 %
10	Purified water	95 %

5 % Solution of metformin hydrochloride is prepared by dissolving metformin hydrochloride into purified water.

# Experiment 1

## 15 Tasting experiment

Tasting experiments on the solutions of Examples 1 to 3 and Reference example 1 were carried out with 20 panelists. The numbers of panelists who felt the solution "not bitter", "a little bitter" and "very bitter" are shown in Table 1.

20 Table 1

	Solution	"not bitter"	"a little bitter"	"very bitter"
	-----			
	Example 1	11	8	1
	Example 2	10	9	1
25	Example 3	11	8	1
	Reference example 1	0	2	18

Tasting experiments on the solutions of Examples 4 to 7 were also carried out, with satisfactory results.

## Experiment 2

Tasting and stability experiments

Tasting and stability experiments on the solutions at various pH of Example 13 were carried out, in the same manner as Experiment 1. A stability experiment was carried out by measuring the remaining amount of metformin in the solutions with HPLC after heating the solutions in vials at 60 °C for 2 weeks. The results are shown in Table 2.

Table 2

pH	taste	remaining amount(%)
2	very sour	78
3	sour	86
3.5	good	94
4	good	96
5	good	98
6	good	100
7	very bitter	98

Metformin hydrochloride is not stable below pH 3.5, and the solution tastes sour. The solution over pH 7 has bitterness.

Normally we feel bitterness most in solution formulation. Therefore these experiments on the solutions indicate that other formulations such as jelly, gum drops, dry syrup, powders, fine granules and granules have less unpleasant tastes as well.

The present invention provides an oral formulation of biguanide with less unpleasant tastes. With this invention, people in every age group, for example, elderly people and little children can easily have sufficient amount of biguanide.

## CLAIMS

1. An oral formulation comprising a biguanide and an organic acid.

5        2. An oral formulation comprising a biguanide, an organic acid and a sweetening agent.

3. An oral formulation according to Claim 2 wherein the sweetening agent is selected from aspartame<sup>TM</sup>, saccharine, saccharine sodium, stevioside and mixtures thereof.

10       4. An oral formulation according to Claim 2 or Claim 3 wherein the ratio (w/w) of the biguanide to the sweetening agent is 1 : 0.001 to 1 : 10

15       5. An oral formulation according to any one of Claims 1 to 4 wherein the biguanide is metformin or the pharmaceutical salt thereof.

6. An oral formulation according to any one of Claims 1 to 5 wherein the organic acid is selected from malic acid, citric acid, tartaric acid and mixtures thereof.

20       7. An oral formulation according to any one of Claims 1 to 6 wherein the ratio (w/w) of the biguanide to the organic acid is 1 : 0.01 to 1 : 50.

8. An oral formulation according to any one of Claims 1 to 7 in the form of a solution, jelly, gum drops, dry syrup, powders, fine granules or granules.

25       9. An oral formulation according to Claims 8 which is in the form of a solution wherein the pH of the solution is 3.5 to 6.

10. An oral formulation according to Claims 8 which is not in the form of a solution and the pH of the solution or dispersion which is formed by dispersing 1 part of the formulation in 10 parts

by weight of water is 3.5 to 6.

# INTERNATIONAL SEARCH REPORT

Interr. Appl. No.

PCT/JP 99/02192

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/155 A61K47/12 A61K47/26

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 21 24 256 A (DR. CHRISTIAN BRUNNENGRÄBER) 30 November 1972 (1972-11-30) page 4; example 1 ---	1
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Y	EP 0 390 369 A (AMERICAN HOME PROD) 3 October 1990 (1990-10-03) claims 1,2 --- -/--	1-10



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Fax: (+31-70) 340-3016

Authorized officer

Herrera, S

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PATENT ABSTRACTS OF JAPAN vol. 010, no. 120 (C-343), 6 May 1986 (1986-05-06) & JP 60 246325 A (TAKEDA YAKUHI KOGYO KK), 6 December 1985 (1985-12-06) abstract -----	1-10
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